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Prediction of ankylosing spondylitis in the population-based HUNT study by a genetic risk score combining 110 SNPs of genome-wide significance

Authors: Sina Rostami <https://orcid.org/0000-0003-2667-3927>, Mari Hoff <https://orcid.org/0000-0002-9992-8663>, Matthew A. Brown <https://orcid.org/0000-0003-0538-8211>, Kristian Hveem <https://orcid.org/0000-0001-8157-9744>, Oddgeir L. Holmen, Lars G. Fritsche <https://orcid.org/0000-0002-2110-1690>, Vibeke Videm <https://orcid.org/0000-0002-1042-3889>

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Institutions: Department of Clinical and Molecular Medicine, Department of Neuromedicine and Movement Science, and Department of Public Health and Nursing, Faculty of Medicine and Health Sciences, NTNU - Norwegian University of Science and Technology, Trondheim, Norway; and Department of Rheumatology and Department of Immunology and Transfusion Medicine, St. Olavs University Hospital, Trondheim, Norway; and Institute of Health and Biomedical Innovation, Translational Research Institute, Princess Alexandra Hospital, Queensland University of Technology, Brisbane, Australia; and Department of Biostatistics and Center for Statistical Genetics, University of Michigan, Ann Arbor, USA

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Author information:

Sina Rostami (SR), MSc, PhD Candidate, Department of Clinical and Molecular Medicine, NTNU - Norwegian University of Science and Technology.

Mari Hoff (MH), MD, PhD, Rheumatologist, Associate Professor, Department of Rheumatology, St. Olavs University Hospital, Trondheim, Norway; Department of Neuromedicine and Movement Science, & Department of Public Health and Nursing, NTNU - Norwegian University of Science and Technology.

Matthew A. Brown (MAB), MBBS, MD, FRACP, FAHMS, FAA, Director of Genomics, Institute of Health and Biomedical Innovation, Translational Research Institute, Princess Alexandra Hospital, Queensland University of Technology, Brisbane, Australia.

Kristian Hveem (KV), MD, PhD, Professor, KG Jebsen Center for Genetic Epidemiology, NTNU - Norwegian University of Science and Technology.

Oddgeir L. Holmen (OLH), MD, PhD, Researcher, KG Jebsen Center for Genetic Epidemiology, NTNU - Norwegian University of Science and Technology.

Lars G. Fritsche (LGF), PhD, Assistant Research Scientist, KG Jebsen Center for Genetic Epidemiology, NTNU - Norwegian University of Science and Technology; Department of Biostatistics and Center for Statistical Genetics, University of Michigan, Ann Arbor, USA.

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Vibeke Videm (VV), MD, PhD, Professor, Department of Clinical and Molecular Medicine, NTNU - Norwegian University of Science and Technology & Department of Immunology and Transfusion Medicine, St. Olavs University Hospital.

Corresponding author:

Vibeke Videm, MD, PhD

Department Clinical and Molecular Medicine,

Lab Center 3 East

St. Olavs Hospital

NO-7006 Trondheim

Norway

Tel: +47 72 57 33 21

Fax: +47 72 57 64 26

E-mail: vibeke.videm@ntnu.no

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Abstract

Objective: The genetic component of ankylosing spondylitis (AS) development is ~90%. Of the known heritability, ~20% is explained by *HLA-B27*, and 113 identified AS-associated SNPs account for ~7.4%. The objectives were to construct a weighted genetic risk score (wGRS) using currently known genome-wide susceptibility SNPs, and evaluate its predictive ability for AS in the Norwegian population-based Nord-Trøndelag Health Study (HUNT).

Methods: AS cases (n=164) and controls (n=49,032) were from the second (1995-1997) and third (2006-2008) waves of the HUNT study, to which the entire adult population of the northern region of Trøndelag was invited. A wGRS based on 110 SNPs weighted by published odds ratios for AS was constructed, representing each person's carriage of all risk variants. Logistic regression models including the wGRS alone or in combination with *HLA-B27* carrier state and other adjustment variables (gender, age, smoking, body mass index, and hypertension) were developed.

Discrimination among models was compared using area-under-the-curve (AUC).

Results: The wGRS was associated with AS (OR: 1.7; 95% CI: 1.4-2.1), but showed low discrimination (AUC: 0.62 (0.58-0.67)). *HLA-B27* was significantly associated with AS (OR: 50(32-81), showing high discrimination (AUC: 0.88 (0.85-0.90)).

Combining the wGRS and *HLA-B27* improved prediction (AUC: 0.90 (0.87-0.92)), $p < 0.001$ vs. wGRS alone, $p < 0.01$ vs. *HLA-B27* alone). Further inclusion of adjustment variables gave a small improvement (AUC: 0.91 (0.89-0.94), $P = 0.03$).

Conclusion: Prediction in a population-based setting based on all currently known AS susceptibility SNPs was better than *HLA-B27* carrier state alone, although the improvement was small and of uncertain clinical value.

Spondylarthritis (SpA) refers to a group of immune-mediated inflammatory rheumatic diseases showing common genetic and clinical features. Ankylosing spondylitis (AS) is an axial SpA characterized by structural changes in the sacroiliac joints (1) and spine (2). AS is associated with disability and reduced quality of life (3). The prevalence is estimated to 23.8 per 10,000 persons in Europe (4).

The etiology of AS is only partly understood. The genetic component of AS development is estimated from twin studies to be around 90% (5), which is higher than in other rheumatic diseases such as rheumatoid arthritis (6). About 20% of the known heritability for AS is attributed to *HLA-B27* and about 7.4% to 113 SNPs found in association studies (7). Thus, approximately 60% of the heritability is probably determined by as yet unmapped variants.

A genetic risk score (GRS) is a multi-locus profile of genetic risk, which may be used to study complex diseases in population health research (8). GRS models could help earlier identification of people at increased risk of developing the disease, potentially permitting prevention or earlier treatment. Such models may also be developed to estimate the probability of the disease outcome on the population level (9). The hypothesis for the present study was that despite the current knowledge regarding almost 30% of the heritability for AS, disease prediction on a population level would be imprecise. We further hypothesized that inclusion of non-genetic variables would give a significant improvement of prediction.

The aims of the current study were to construct a genetic risk score based on

association study on AS to date (7), and to evaluate its predictive ability for AS in combination with relevant non-genetic variables in a population-based setting with data from the Nord-Trøndelag Health Study (HUNT). Finally, we wanted to evaluate whether addition of validated SNPs for AS from other studies could improve prediction.

Patients and methods

In HUNT, the entire adult population (≥ 20 yrs) of the northern region of Trøndelag (previously, Nord-Trøndelag county) in Norway was invited to participate. Data were collected from participants through questionnaires, interviews, clinical examinations, and blood sampling (10). The present study is based on data from the second (HUNT2; 1995-1997) and third (HUNT3; 2006-2008) HUNT surveys (10). Figure 1 summarizes the inclusion of participants. AS in HUNT2 and HUNT3 was diagnosed using the Modified New York Criteria (11), as part of the ongoing HuLARS study (**H**unt **L**ongitudinal **A**nkylosing spondylitis and **R**heumatoid arthritis Study) (12). Cases for whom the diagnosis was not reliably established, and those diagnosed with psoriatic arthritis, juvenile inflammatory arthritis, or other inflammatory arthritis were excluded. Some clinical data were not sufficient for an accurate diagnosis of non-radiographic axial SpA, so these cases were excluded and AS was defined as the phenotype of interest.

The HUNT study was approved by the Regional Committee for Medical and Health Research Ethics (REK), the Norwegian Data Inspectorate, and the National Directorate of Health. All participants gave written informed consent, and the study

was performed in accordance with the Helsinki declaration. The HuLARS study was approved by REK (REK Midt 2009/661), and the Norwegian Data Inspectorate.

Genotyping and imputation

SNPs analyzed in our study were genotyped utilizing the HumanCoreExome arrays from Illumina Inc. (HumanCoreExome12 v1.0, HumanCoreExome12 v1.1 and UM HUNT Biobank v1.0). Genotyping was performed at the NTNU Genomics core facility, Trondheim, Norway. Further details including quality control have been given previously (13). Imputation was performed using Minimac3 (v2.0.1, <http://genome.sph.umich.edu/wiki/Minimac3>) (14). Only samples of recent European ancestry were used, defined as samples falling into an ellipsoid exclusively spanning European populations of the Human Genome Diversity Project reference panel (15). A merged reference panel was constructed by combining the Haplotype Reference Consortium panel (release version 1.1) (16) and a reference panel from 2,202 whole-genome sequenced HUNT study participants.

Risk scores and statistical analysis

Genetic risk variants for AS were identified from English-language literature available on PubMed until 27.05.2018 that reported SNPs from large case-control studies in Caucasians. Inclusion criteria were that the association to AS was confirmed in a meta-study, in several independent studies, or documented both in a discovery and validation cohort. We included the most recent and comprehensive GWAS meta-study for five chronic inflammatory diseases including AS (7), which used a combination of a subset-based statistical approach to achieve genome-wide significance ($p < 5 \times 10^{-8}$), and Bonferroni-correction for the actual number of linkage

disequilibrium-independent markers analyzed. For SNPs from other studies, we set the p-value for inclusion at $p \leq 5 \times 10^{-6}$ and performed a sensitivity analysis using $p \leq 5 \times 10^{-8}$. In total, we had access to 148 previously identified susceptibility SNPs for AS from five studies (Supplement). This included 110 SNPs from the mentioned GWAS meta-study (7), denoted as “GWAS SNPs” in the following text, and 38 from other studies (denoted as “additional SNPs”, Supplement). First, the 110 GWAS SNPs were used to construct a weighted genetic risk score (hereafter denoted wGRS110) by the addition of risk alleles and weighting by the natural logarithm of the published OR, representing each person’s carriage of all risk variants. *HLA-B27* carrier state (positive/negative) was not included in the score but was used as a separate variable, based on the genotypes of rs4349859.

Second, an additional weighted genetic risk score from a reduced set of the additional 38 SNPs was constructed (hereafter denoted wGRS15) (Supplement). To this end, linkage disequilibrium was evaluated of those SNPs on each chromosome fulfilling the initial p-value criterion ($p \leq 5 \times 10^{-6}$) using LDlink (<https://analysistools.nci.nih.gov/LDlink/>). 19 SNPs closely linked to other SNPs (defined as $r^2 > 0.8$) were first removed by the following selection strategy: In case of close linkage of additional SNPs with GWAS SNPs, the additional SNPs were omitted. In case of close linkage among the additional SNPs, we kept the non-linked SNPs with the highest OR for the association with AS. The biggest possible SNP set was selected, and finally consisted of 15 SNPs that were used to calculate the wGRS15 (Supplement). For the sensitivity analysis with a risk score based on genome-wide significance, the same strategy was used and resulted in a selection of

8 SNPs that were not closely linked. These were included in the wGRS8. All three wGRS were used as continuous variables in logistic regression modelling.

Baseline information on sex, age (age ≤ 30 or > 60 years; versus age > 30 or ≤ 60 years), smoking (current, former, or never smoker), body mass index (BMI), and hypertension was used as adjustment variables in the logistic regression analysis. BMI was calculated as weight (kg)/height (m)². Hypertension was defined as either a “yes” response to the question “Are you using medication for high blood pressure”, or measurement of systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg. An additional indicator variable denoting whether the individual’s baseline data were recorded at HUNT2 or HUNT3 (i.e. the first of these waves the person participated in) was also included in the models. Linearity of logits was evaluated by plots. The Hosmer-Lemeshow test was used to evaluate model fit, and the area (AUC) under the receiver operating characteristics (ROC) curve was used to assess discrimination. The Akaike information criterion (AIC) and Bayesian information criterion (BIC) were employed to compare the fit of alternative models. For the best model, the point on the ROC curve with the highest sensitivity and specificity was calculated using the Youden index. The sensitivity, specificity, and positive and negative predictive values (PPV and NPV) using this point as a cut-off were then calculated. Data were analyzed using Stata (version 14.1, StataCorp, College Station, Texas, USA). Data are given as mean \pm SD or OR (95% CI) unless otherwise stated. P-values < 0.05 were considered statistically significant.

The main analysis was performed on a dataset that was complete for adjustment

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containing either wGRS110 or *HLA-B27* alone, respectively. Model 3 included both wGRS110 and *HLA-B27*. Models 4 and 5 included wGRS110, *HLA-B27*, and adjustment variables (gender, age, smoking, BMI, and hypertension), and model 5 further included wGRS15. An alternative model 5 exchanged wGRS15 with wGRS8.

Additionally, two sensitivity analyses were performed using a similar modelling approach. The first of these sensitivity analyses was done following multiple imputation of adjustment variables to account for missing data, using chained equations (n=50 datasets) and assuming missing at random. The second sensitivity analysis was performed after removal of all participants who showed a 2nd degree or closer family relationship (Figure 1) to account for potential relationship bias. In the second sensitivity analysis, kinship coefficients were estimated using KING with a cutoff at estimated kinship coefficient 0.0884, which corresponds to the upper bound of 2nd degree relatives (<http://people.virginia.edu/~wc9c/KING>). A set prioritizing AS cases was selected by preferably omitting controls where possible. The final set comprised 147 AS cases and 13,052 controls.

Results

Table 1 summarizes baseline characteristics of the study participants.

The wGRS110 ranged from 10.93 to 17.29. The median wGRS110 was 14.60 (interquartile range (IQR): 14.11-15.08) in AS cases and 14.26 (IQR: 13.73-14.78) in the controls.

There was substantial overlap in the wGRS110 distribution between cases and controls (Figure 2).

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Table 2 summarizes the five logistic regression models from the main analysis. The Hosmer-Lemeshow test showed good fit for all models. wGRS110 was significantly associated with AS (model 1, OR=1.7 (1.4-2.1) for one unit increase, $p<0.001$). However, the discriminative ability of this model was low (Figure 3). *HLA-B27* showed the highest OR, whether as single explanatory variable (model 2, OR=50; 95% CI: 32-81) or with other predictors (models 3-5). All models including *HLA-B27* had high discriminatory ability with AUC >0.88 (Figure 3). The model combining wGRS110 and *HLA-B27* (model 3) had a higher AUC compared to the univariate models with either wGRS110 ($p<0.001$) or *HLA-B27* ($p<0.01$). Further inclusion of adjustment variables (age, gender, smoking, BMI, and hypertension) to the model including wGRS110 and *HLA-B27* significantly improved the discriminative ability (model 4, $p=0.03$ vs. model 3). Further addition of wGRS15 to model 4 did not improve the discriminative ability (model 5, $p=0.54$ vs. model 4, Table 2 and Figure 3). However, wGRS15 was a significant variable when included in models without wGRS110, whether alone (OR=1.64(1.17-2.31)) or together with *HLA-B27* and the adjustment variables (OR=1.74(1.24-2.46)). AIC and BIC values for models 1-5 are summarized in Figure 3. Based on the combined AIC and BIC values, model 4 including wGRS110, *HLA-B27*, and adjustment variables was the most parsimonious model with best fit. The results were essentially unchanged when wGRS8 (Supplement) was used instead of wGRS15 (data not shown). When the point on the ROC curve for model 4 with highest sensitivity (88%) and specificity (88%) was used as cut-off for a positive vs. negative test for AS, the NPV was 100% and the PPV was 2.3%.

After repeating the analyses following imputation of missing data for the adjustment variables in the first sensitivity analysis, most results were very similar (Table S1). A notable difference was that wGRS15 was significant when included in model 5 (OR 1.5(1.1-2.1), $p=0.024$). Following removal of participants to select a dataset without 2nd degree or closer family relationships in the second sensitivity analysis ($n=13,199$) there were very small changes from the original analysis (Table S2).

Discussion

In this large population-based study of AS cases and non-AS controls, high discriminatory ability was seen with *HLA-B27* and even higher when a wGRS based on most of the currently known risk SNPs for AS was also considered.

Unsurprisingly, the discriminatory capacity of the wGRS alone was much lower than the *HLA-B27* carrier state. Prediction was slightly improved by addition of adjustment variables, reaching an AUC of 0.91 for the multivariable model.

The results are in accordance with the high genetic component of AS development as well as the relative attribution of the known heritability for *HLA-B27* and the other previously identified SNPs, respectively (7). In the main analysis, addition of a wGRS based on 15 further validated risk SNPs (wGRS15) gave no improvement even if this score was significantly associated with AS as a single predictor.

However, in the sensitivity analysis following imputation of missing adjustment variables, wGRS15 gave a significant contribution to overall prediction. This may be due to increased power with inclusion of more AS cases. The study therefore suggests that the large proportion of undetermined genetic risk variants may play a

substantial role for prediction. For better prediction, it seems like discovery and

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inclusion of many more genetic risk variants, or the use of more efficient statistical

approaches such as genome-wide risk score development would be necessary. Furthermore, inclusion of information on rare variants, copy number variants, epigenetic factors, other demographic factors, and interactions terms may be required.

A risk score-based predictive model for AS in a South Korean study used *HLA-B27*, three copy number variants, and one SNP, and found higher specificity and accuracy compared to the *HLA-B27* only model (17). The authors reported an AUC of 0.98 and 0.95 for the construction and validation datasets of the final model, respectively. This is higher than for our models. However, the two studies have major differences: They are based on populations with different ethnicities (East Asian vs. Caucasian) with their distinctive genetic compositions, and the studied type of variations differed (copy number variants and SNP). The present study was performed in a population-based setting with a less selected control group, which may reduce bias. We also included a larger number of risk SNPs, as well as demographic and clinical data.

A potential source of error in the present study could be relatedness among participants. However, there were small changes in the OR after removal of close relatives, demonstrating that relatedness had very little impact on the predictive ability of the wGRS. This suggests that even for a disease with substantial heritability, it may not be necessary to account for kinship when testing the predictive ability of a wGRS, and that removal of close relatives may lead to unnecessary loss of cases.

The aim of our study was not to develop a clinical prediction model for AS.

Although AUC is a measure of sensitivity and specificity of the disease, the clinical population-level outcome is influenced by the disease prevalence and heritability (18). The models in the current study had relatively high AUC of up to 0.91.

However, due to the low AS prevalence in Europe (4), the current models would not be useful on an individual level because the PPV (i.e. the probability of having AS given a high score) was very low. This is in accordance with a previous study showing that genetic data did not perform better than clinical data in back pain patients with suspected axial SpA (19). On the other hand, a negative test based on model 4 had an excellent NPV. Even so, we find that a genetic risk score with a higher PPV should be sought for before such a test is included in clinical practice for population screening.

To our knowledge, this is the largest general population-based study yet conducted to test the predictive ability of a genetic risk prediction model for AS in the Caucasian population. Several studies have been performed with other aims, among them a prediction of AS radiographic severity (20), response to TNF- α blocking therapy in AS (21), and prediction of cardiovascular events among those with AS (22). The number of AS cases in our cohort was too low to investigate such research questions.

The pathogenesis of AS is still not well elucidated. A previous study from HUNT showed significant associations of present smoking, hypertension, and younger age, but not of BMI, with the incidence of AS (23). In our study, inclusion of adjustment

variables in addition to *HLA-B27* and *wGRS110*, significantly improved prediction, Downloaded from www.jrheum.org on February 21, 2020 - Published by [The Journal of Rheumatology](#)

probably mostly due to statistical adjustment for imbalances in age and gender between cases and controls. The increase in AUC was numerically small, however, again underscoring the importance of the strong genetic component of AS. It would have been interesting to test potential model improvement from inclusion of AS-related variables like disease activity scores or the patients' own evaluation. Such variables were not available, and rarely are in a population-based study, especially for controls.

Risk variants found in GWAS are not necessarily causative. Previous research has shown that weighted risk scores are relatively robust to the influence from non-causative SNPs, regardless of the strength of linkage disequilibrium they have to causative SNPs (24). Furthermore, the main aim of risk prediction is to reach a high predictive power, and to increase the validity and robustness of model predictions. This does not necessitate inclusion only of causal associations (9).

The study has some limitations. Despite efforts to ascertain the AS diagnoses in HUNT (12), there could be false positive or false negative cases, which would reduce predictive accuracy. There is also a potential for selection bias of participants in HUNT. Our models were not validated in another cohort. Furthermore, genetic predictive medicine is in its infancy and has several ethical challenges when used in individuals because of the complicated disease mechanisms. We also cannot exclude that a comparable risk score based on SNPs associated with the risk for AS in other populations or ethnicities may perform better due to different genotype frequencies and phenotypic effect sizes (25). The high frequency of women among the new AS

cases in HUNT3 may be due to an increased awareness of AS not only as a disease

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in men, as well as selection bias to HUNT because a relatively lower proportion of the invited young men than young women participated (12).

In conclusion, prediction in a population-based setting based on all currently known AS susceptibility SNPs was better than *HLA-B27* alone, although the improvement was not major and of uncertain clinical value.

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The HUNT study is a collaboration between HUNT Research Centre (Faculty of Medicine and Health Sciences, NTNU – Norwegian University of Science and Technology), Nord-Trøndelag County Council, Central Norway Health Authority, and the Norwegian Institute of Public Health.

Some results from the present study were presented at the Annual European Congress of Rheumatology - EULAR (12-15th June 2018, Amsterdam) (26).

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Figure 1: Participant inclusion

Inclusion of participants for risk prediction models for ankylosing spondylitis (AS) in the population-based HUNT study in the Nord-Trøndelag area, Norway.

HUNT2 and HUNT3 are two waves of HUNT, conducted in 1995-1997 and 2006-2008, respectively.

Figure 2: Risk score distribution in AS cases and controls

Distributions of weighted genetic risk score wGRS110 based on 110 susceptibility SNPs for ankylosing spondylitis (AS) reported in (7).

Figure 3: Discrimination by logistic regression models

Area under receiver operating characteristics curves for five models. Model 1: risk score for 110 ankylosing spondylitis (AS) susceptibility SNPs (wGRS110) only; Model 2: *HLA-B27* (positive/negative) only; Model 3: wGRS110 and *HLA-B27*; Model 4: wGRS110, *HLA-B27*, and adjustment variables (age, gender, smoking, body mass index, hypertension); Model 5: wGRS110, *HLA-B27*, risk score for 15 additional AS susceptibility SNPs (wGRS15) and adjustment variables as in model 4. AUC: area under the curve with 95% confidence interval in parenthesis. Akaike (AIC) and Bayesian (BIC) information criteria for models shown.

Table 1. Baseline characteristics of study participants

	HUNT2 (n=39,782)		HUNT3 (n=9,414) ¹	
	AS cases (n=142)	Controls (n=39,640)	AS cases (n=22)	Controls (n=9,392)
<i>HLA-B27</i> , % positive	88.7	12.5	81.8	12.6
Age, mean ± SD	41.9±11.1	47.4±17.2	43±10.6	40.4±14.8
Women, %	37	53	64	53
Smoking, %				
Never smoker	40	45	54	52
Previous smoker	28	23	23	25
Current smoker	32	32	23	23
Body mass index (kg/m ²), mean ± SD	26.3±4.2	26.2±4.1	27.2±5	26.6±4.7
Hypertension, %	35	40	27	22

AS: ankylosing spondylitis; HUNT: Nord-Trøndelag Health Study, wave 2 or 3

¹Novel participants who did not participate in HUNT2

Table 2. Logistic regression models for weighted genetic risk scores (wGRS) for AS¹

Model	wGRS110 ² (OR(95%CI); P-value)	wGRS15 ² (OR(95%CI); P-value)	<i>HLA-B27</i> (OR(95%CI); P-value)	Male gender (OR(95%CI); P-value)	Age ³ (OR(95%CI); P-value)
Model 1	1.7(1.4-2.1); <0.001	-	-	-	-
Model 2	-	-	50(32-81); <0.001	-	-
Model 3	1.8(1.4-2.2); <0.001	-	51(32-81); <0.001	-	-
Model 4 ⁴	1.8(1.4-2.1); <0.001	-	51(32-82); <0.001	1.7(1.2-2.3); 0.002	3.3(2.2-4.9); <0.001
Model 5 ⁴	1.7(1.4-2.1); <0.001	1.4(1.0-2.0); 0.068	52(32-82); <0.001	1.7(1.2-2.3); 0.002	3.3(2.2-4.9); <0.001

¹ 164 ankylosing spondylitis (AS) cases and 49,032 controls

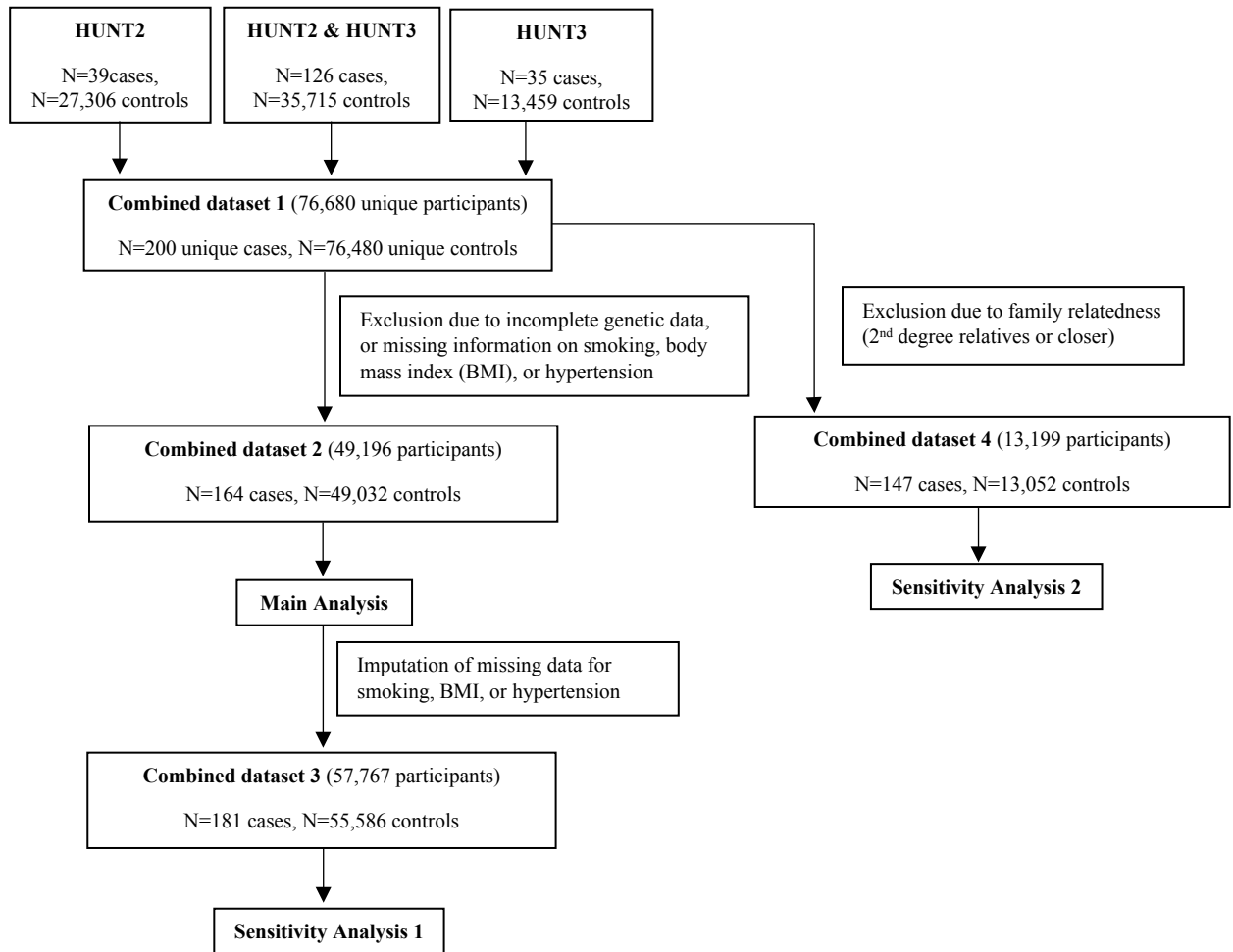
² wGRS110 and wGRS15 are weighted genetic risk scores for AS, based on 110 and 15 risk SNPs, respectively

³ Baseline age (age ≤30 or >60 years versus age >30 or ≤60 years)

⁴ Models were also adjusted for baseline smoking (current, former, or never smoker), body mass index, and hypertension

- Variable was not included in the model

Figure 1



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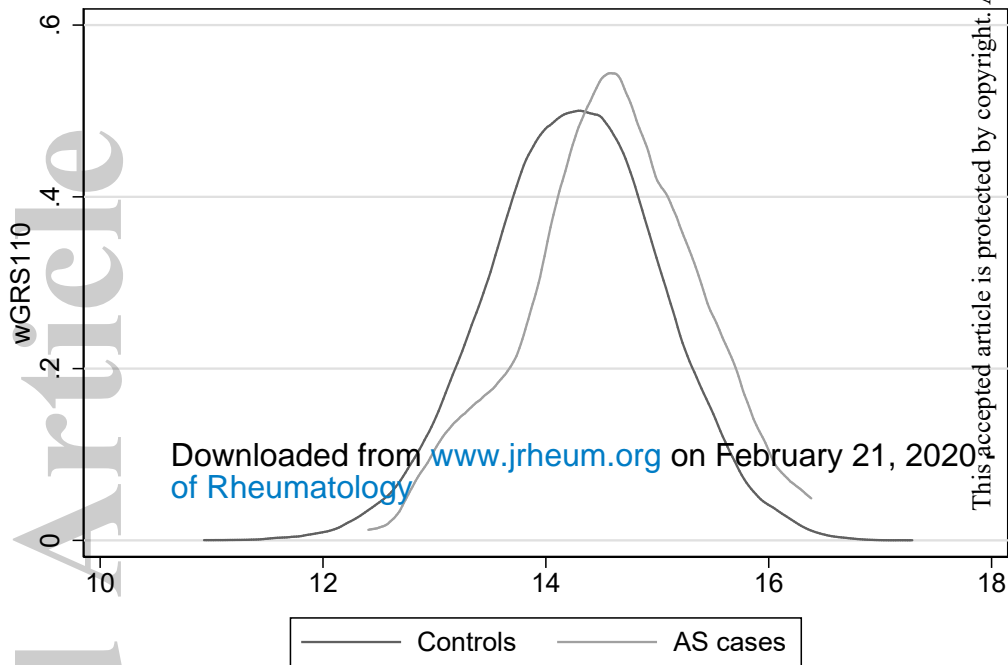
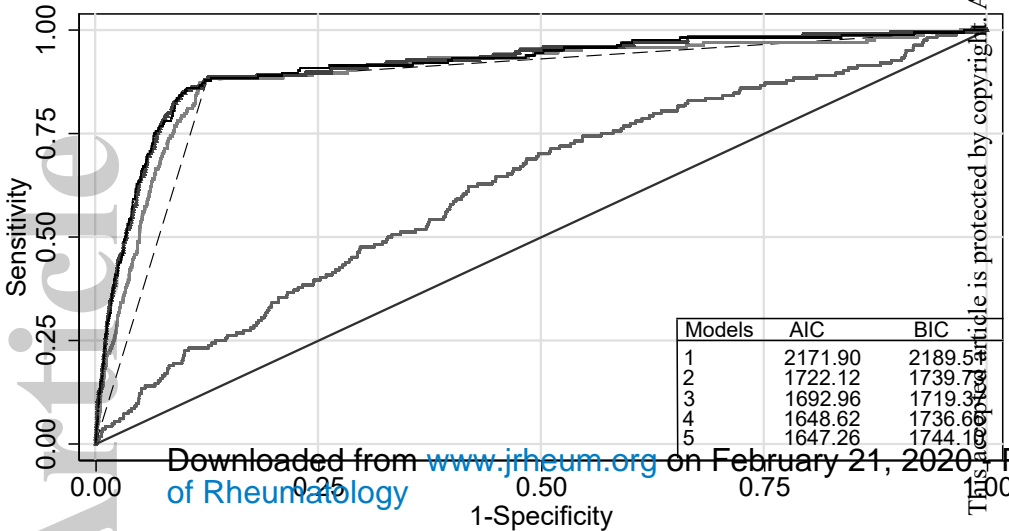


Figure 3
Page 25 of 25



Model 1 AUC: 0.62(0.58-0.67)	Model 2 AUC: 0.88(0.85-0.90)
Model 3 AUC: 0.90(0.87-0.92)	Model 4 AUC: 0.91(0.89-0.94)
Model 5 AUC: 0.91(0.89-0.94)	Reference

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